PTO/SB/21 (02-04) Approved for use through 07/31/2006. OMB 0651-0031 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE are required to respond to a collection of information unless it displays a valid OMB control number. 1995, no persons Application Number 10/705,282 Filing Date TRANSMITTAL 11/10/2003 **FORM** First Named Inventor Chackalamannil Art Unit 1625 (to be used for all correspondence after initial filing) **Examiner Name** To Be Assigned **Attorney Docket Number** CV01185K1X Total Number of Pages in This Submission **ENCLOSURES** (Check all that apply) After Allowance communication Fee Transmittal Form Drawing(s) Appeal Communication to Board Licensing-related Papers Fee Attached of Appeals and Interferences Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) Petition Amendment/Reply Petition to Convert to a **Proprietary Information** After Final **Provisional Application** Power of Attorney, Revocation Status Letter Affidavits/declaration(s) Change of Correspondence Address Other Enclosure(s) (please Terminal Disclaimer **Extension of Time Request** Identify below): Request for Refund **Express Abandonment Request** Form PTO 1449 (2); References (29); CD, Number of CD(s) Post Card Information Disclosure Statement Remarks Certified Copy of Priority Document(s) Response to Missing Parts/ Incomplete Application Response to Missing Parts under 37 CFR 1.52 or 1.53 SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT Firm Individual name Gerard E Reinhardt / Reg. No. 43,041 Signature Date July 28, 2004 CERTIFICATE OF TRANSMISSION/MAILING I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below. Typed or printed name Gerard E. Reinhardt Date Signature July 28, 2004 This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to

process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandriá, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PATENT CV01185K1X



In re Application of:

Examiner: To Be Assigned

S. Chackalamannil et al

Group Art Unit: 1625

Serial No.: 10/705,282

Filing date: 11/10/2003

: Attorney Docket No.: CV01185K1X

For: "Methods of Use of Thrombin

Receptor Antagonists"

Commissioner for Patents P. O. Box 1450

Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

It is requested that the following documents cited in the specification of the subject application, as listed below and in the accompanying form PTO-1449, be considered and made of record.

Patent:

WO 01 00576 A1 WO 01 00656 A2 WO 01 00657 A2 WO 01 00659 A1 WO 02 071847 A1 WO 02 076965 A1 WO 02 085850 A1 WO 02 088092 A1

Publications:

Ahn, Ho-Sam, Nonpeptide thrombin receptor antagonists, *Drugs of the Future*, 26(11), (2001)pp. 1065-1085.

Chan, Barden et al., Antiangiogenic property of human thrombin, Microvascular Research, (2003), 66(1), pp. 1-14.

Chang, M.C. et al., Thrombin-stimulated growth, clustering, and collagen lattice contraction of human gingival fibroblasts is associated with its protease activity, Journal of Periodontology, (2001), 72(3), pp. 303-13.

Chambers, R.C. et al., Coagulation cascade proteases and tissue fibrosis, *Biochemical Society Transactions*, 30(2), (2002), pp. 194-200.

Cunningham, Malcolm A. et al., Protease-activated Receptor 1 Mediates Thrombin-dependent, Cell-mediated Renal Inflammation in Crescentic Glomerulonephritis, *J. Exp. Med*, Vol. 191, No. 3, Feb. 7, 2000, pp 455-461.

D'Andrea, Michael R. et al, Expression of protease-activated receptor-1,-2,-3 and —4 in control and experimentally inflamed mouse bladder, *American Journal of Pathology*, 2003, 162(3), pp. 907-923.

Even-Ram, Sharona et al., Thrombin receptor overexpression in malignant and physiological invasion processes, *Nature Medicine*, Vol. 4, No. 8, (1998) pp.909-914.

Heckert, Olaf, et al., Sex Steroids Used in Hormonal Treatment Increase Vascular Procoagulant Activity by Inducing Thrombin Receptor (PAR-1) Expression, *Circulation*, (2001), 104, pp.2826 – 2831.

Jurk, Kerstin et al., Loss of Intact Seven-Transmembrane-Thrombin Receptor on the Platelet Surface of Patients with Acute Ischemic Stroke, *Circulation*, Vol. 98, 17S Abstract #2382, (1998) pp. I-453.

Kaufmann, R. et al., Meizothrombin, an intermediate of prothrombin cleavage potently activates renal carcinoma cells by interaction with PAR-type thrombin receptors, *Oncology Reports*; 10 (2), (2003) pp. 493-496.

Meli, Rosaria et al., Thrombin and PAR-1 activating peptide increase iNOS expression in cytokine-stimulated C6 glioma cells, *Journal of Neurochemistry*, 79(3), (2001), pp. 556-563.

Nguyen, Quang-De et al., RhoA- and RhoD-dependent regulatory switch of $G\alpha$ subunit signaling by PAR-1 receptors in cellular invasion, *FASEB Journal*, 2002, 16(6), pp. 565-576.

Remenar, Julius F., et al. Crystal Engineering of Novel Cocrystals of a Triazole Drug with 1,4-Dicarboxylic Acids, *J. A. Chem. Soc.*, Vol. 125 No. 8, (2003), pp. 8456-8457.

Roche, Nicolas et al., Effect of acute and chronic inflammatory stimuli on expression of protease-activated receptors 1 and 2 alveolar macrophages, *Journal of Allergy and Clinical Immunology*, 111(2), (2003), pp. 367-373.

Schiller, H. et al., Thrombin as a survival factor for cancer cells: thrombin activation in malignant effusions in vivo and inhibition of idarubicin-induced cell death in vitro, *Int'l. J. of Clinical Pharmacology and Therapeutics*, 40(8), (2002), pp. 329-335.

Strukova, S.M. et al., Thrombin, a regulator of reparation processes in wound healing, *Bioorganicheskaya Khimiya*, 24(4), (1998), pp. 288-292.

Tanaka, Nobuhisa et al., Thrombin-induced Ca²+ mobilization in human gingival fibroblasts is mediated by protease-activated receptor-1(PAR-1), *Life Sciences* 73 (2003), pp. 301-310.

Tellez, Carmen et al., Role and regulation of the thrombin receptor (PAR-1) in human melanoma, *Oncogene* 22, (2003) pp. 3130-3137.

Tognetto, Michele et al., Proteinase-activated receptor-1(PAR-1) activation contracts the isolated human renal artery <u>in vitro</u>, *British Journal of Pharmacology*, 139 (1), (2003) pp. 21-27.

Vogel, S.M. et al., Abrogation of thrombin-induced increase in pulmonary microvascular permeability in PAR-1 knockout mice, *Physiol Genomics*, 4(2), (2000) pp. 137-145.

Wang, Junru et al., Deficiency of microvascular thrombomodulin and up-regulation of protease-activated receptor-1 in irradiated rat intestine: possible link between endothelial dysfunction and chronic radiation fibrosis, *American Journal of Pathology*, 160(6), (2002) pp. 2063-72.

The submission of these documents is not to be presumed as an admission that these documents are prior art. The documents are being furnished solely for their possible utility in the examination of the present case. Since no Office Action has issued on the merits of this case, Applicants believe that no fee is due at this time. If, however, any fees are due, the Office may charge such fees to Deposit Account No. 19-0365. If the Examiner has any questions, the Examiner is invited to contact the undersigned

Schering-Plough Corporation 2000 Galloping Hill Road Patent Department, K-6-1,1990 Kenilworth, NJ 07033

Tel: (908) 298-2960 Fax: (908) 298-5388

Respectfully submitted

Gerard E. Rein/hardt Attorney for Applicants

Reg. No. 43,041 July 28, 2004

FORM PTO-1449

U.S. PARTMENT OF COMMERCE TRAINENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT
BY APPLICANT

ATTY. DOCKET NO.: APPLICATION NO.: CV01185K1X 10/705,282 APPLICANT:

S. Chackalamannil et al

	BY APPLICANT				5. Chackalamannii et al				
(Use several sheets if necessary)				ary)	FILING DATE: 11/10/2003		GROUP: 1625		
-			U.S. PA	ATENT DOCUM	MENTS				
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAN	IE .	CLASS	SUB- CLASS	FILING APPRO	
			l			l	L	<u> </u>	
		F	OREIGN	PATENT DOC	UMENTS				
Ī		DOCUMENT	DATE	COUNTRY		CLASS	SUB-	TRANS	LATIO
		NUMBER					CLASS	YES	NO
	AA	WO 01 00576 A1	01/04/01	WIPO					
	AB	WO 01 00656 A2	01/04/01	WIPO					
	ĀC	WO 01 00657 A2	01/04/01	WIPO					
	AD	WO 01 00659 A1	01/04/01	WIPO					
	AE	WO 02 071847 A1	09/19/02	WIPO					7
	AF	WO 02 076965 A1	10/03/02	WIPO					
	AG	WO 02 085850 A1	10/31/02	WIPO					X
	AH	WO 02 088092 A1	11/07/02	WIPO					X
		07.150.000.00		A ÷	D. I. D. C.		- 4 - \		
		OTHER DOCUM	ENTS (Inclu	iding Author, Title,	Date, Pertinen	Pages, I	=tC.)	00 (44	· -
	Αl	Ahn, Ho-Sam et al.,		thrombin recepto	r antagonists, <i>L</i>	rugs of ti	ne i-uture	, 26 (11),
		(2001): pp. 1065 – 1			0	A 4'			00/41
	AJ	Chan, Barden et al.,	Antianglog	enic property of ni	ıman thrombin,	Microvas	cular Res	searcn,	00(1)
	A 1.	(2003), pp. 1 – 14.	1			-11 1-	Hiss sont	raction	<u>-</u>
İ	AK	Chang, M.C.et al., Thrombin-stimulated growth, clustering, and collagen lattice contract human gingival fibroblasts is associated with its protease activity, <i>Journal of Periodonto</i> .					nacion	,	
				sociated with its p	rolease activity,	Journal	oi Periodo	niiology	•
\longrightarrow	A 1	72(3), (2001), pp. 30 Chambers, R.C.et a)3-13.	ion accordo proto	and tingua	fibragia	Diochomi	ical Sec	iotu
	AL				ases and ussue	11010515,	Diochenn	cai Suc	есу
	AM	Transactions, 30(2), Cunningham, Malco	(2002), pp.	Protocco activate	d Pecenter 1 M	ediates T	hrombin-	denend	ent
['	AIVI	Cell-mediated Rena	I Inflammati	on in Crescentic (lomerulonenhr	itie <i>I Fvi</i>	n Med V	aepena al 191 <i>(</i>	31
		(2000), pp 455-461.		on an orescende c	nonici dionepin	103, U. LA		O	
							•		- /,
	ΔNI			ression of Protes	se-Activated Re	centor-1		_4 in C	
	AN	D'Andrea, Michael F	R. et al., Exp	oression of Protea	se-Activated Re	ceptor-1,	-2,-3 and	-4 in C	ontrol
	AN	D'Andrea, Michael F and Experimentally	R. et al., Exp	oression of Proteat ouse Bladder, <i>Amo</i>	se-Activated Re erican Journal o	ceptor-1, f Patholo	-2,-3 and	-4 in C), (2003	ontrol
		D'Andrea, Michael F and Experimentally 907-923.	R. et al., Exp Inflamed Mo	ouse Bladder, Am	erican Journal c	f Patholo	-2,-3 and gy, 162(3), (2003	ontrol
	AN AO	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona	R. et al., Exp Inflamed Mo a, et al., Thr	ouse Bladder, Amo	erican Journal o	f Patholo malignar	-2,-3 and gy, 162(3), (2003	ontrol
	AO	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes,	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med	ouse Bladder, Ame ombin receptor ov dicine, Vol. 4 (8),	erican Journal of erexpression in (1998), pp.909-	f Patholo malignar 914.	-2,-3 and gy, 162(3), (2003 /siologio	ontrol 3), pp.
		D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al.,	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid	ouse Bladder, Ame ombin receptor ov dicine, Vol. 4 (8), ds Used in Hormo	erican Journal of erexpression in (1998), pp.909- nal Treatment li	malignar 914.	-2,-3 and gy, 162(3 nt and phy), (2003 ysiologic Procoag	ontro), pp cal
	AO	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid	ouse Bladder, Ame ombin receptor ov dicine, Vol. 4 (8), ds Used in Hormo	erican Journal of erexpression in (1998), pp.909- nal Treatment li	malignar 914.	-2,-3 and gy, 162(3 nt and phy), (2003 ysiologic Procoag	ontrol 3), pp.
	AO AP	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831.	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid Thrombin R	ouse Bladder, Ame ombin receptor ov dicine, Vol. 4 (8), ds Used in Hormo eceptor (PAR-1) I	erican Journal of erexpression in (1998), pp.909- nal Treatment li Expression, Circ	malignar 914. ncrease \culation, (i	-2,-3 and gy, 162(3 nt and phy/ascular F 2001), Vo	ysiologic Procoagol. 104,	ontrol i), pp. cal julant
	AO	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831. Jurk, Kerstin et al., I	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid Thrombin R	ombin receptor ov dicine, Vol. 4 (8), ds Used in Hormo eceptor (PAR-1) E	erican Journal of erexpression in (1998), pp.909- nal Treatment In Expression, Circ embrane-Throm	malignar 914. ncrease \culation, (i	-2,-3 and gy, 162(3 nt and phy/ascular F2001), Vo	ysiologic Procoag ol. 104,	ontrol i), pp. cal ulant
	AO AP	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831. Jurk, Kerstin et al., I Surface of Patients	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid Thrombin R	ombin receptor ov dicine, Vol. 4 (8), ds Used in Hormo eceptor (PAR-1) E	erican Journal of erexpression in (1998), pp.909- nal Treatment In Expression, Circ embrane-Throm	malignar 914. ncrease \culation, (i	-2,-3 and gy, 162(3 nt and phy/ascular F2001), Vo	ysiologic Procoag ol. 104,	ontrol i), pp. cal ulant
	AO AP AQ	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831. Jurk, Kerstin et al., I Surface of Patients pp. I-453.	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid Thrombin R Loss of Intac with Acute I	ombin receptor over dicine, Vol. 4 (8), dis Used in Hormo receptor (PAR-1) for the Seven-Transment of Seven-Transment of Seven-Transment of Stroke, (Cartine of Seven-Transment of Stroke, (Cartine of Seven-Transment of Seven-Transment of Stroke, (Cartine of Seven-Transment o	erican Journal of erexpression in (1998), pp.909- nal Treatment In Expression, Circ mbrane-Throm Circulation, Vol.	malignar 914. ncrease \ culation, (i bin Recel	-2,-3 and gy, 162(3) It and phy Ascular F 2001), Vo ptor on th	ysiologic Procoagol. 104, e Platel 2382, (*	ontrol i), pp. cal ulant et 1998)
	AO AP	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831. Jurk, Kerstin et al., I Surface of Patients pp. I-453. Kaufmann, R. et al.,	R. et al., Exp Inflamed Mo a, et al., Thr Nature Med Sex Steroid Thrombin R Loss of Intac with Acute I	ombin receptor over dicine, Vol. 4 (8), dis Used in Hormo receptor (PAR-1) for the Seven-Transment of Seven-Transment of Seven-Transment of Stroke, Combin, an intermedia	erican Journal of erexpression in (1998), pp.909- nal Treatment In Expression, Circ imbrane-Throm Circulation, Vol.	malignar 914. ncrease \ culation, (i bin Recel 98, 175 A	-2,-3 and gy, 162(3 and phy ascular F2001), Voptor on the Abstract #	ysiologic Procoagol. 104, e Platel 2382, (*	ontrol i), pp. cal ulant et 1998)
	AO AP AQ	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831. Jurk, Kerstin et al., I Surface of Patients pp. I-453. Kaufmann, R. et al., renal carcinoma cell	R. et al., Explored Modern Report Programme Modern Report Programme Report Report Programme Report R	ombin receptor over dicine, Vol. 4 (8), dis Used in Hormo receptor (PAR-1) for the Seven-Transment of Seven-Transment of Seven-Transment of Stroke, Combin, an intermedia	erican Journal of erexpression in (1998), pp.909- nal Treatment In Expression, Circ imbrane-Throm Circulation, Vol.	malignar 914. ncrease \ culation, (i bin Recel 98, 175 A	-2,-3 and gy, 162(3 and phy ascular F2001), Voptor on the Abstract #	ysiologic Procoagol. 104, e Platel 2382, (*	ontrol i), pp. cal ulant et 1998)
	AO AP AQ	D'Andrea, Michael F and Experimentally 907-923. Even-Ram, Sharona invasion processes, Heckert, Olaf, et al., Activity by Inducing pp.2826-2831. Jurk, Kerstin et al., I Surface of Patients pp. I-453. Kaufmann, R. et al.,	R. et al., Explored Modern Report Programme Modern Report Programme Report Report Programme Report R	ombin receptor over dicine, Vol. 4 (8), dis Used in Hormo receptor (PAR-1) for the Seven-Transment of Schemic Stroke, Combin, an intermedication with PAR-type	erican Journal of erexpression in (1998), pp.909- nal Treatment In Expression, Circ imbrane-Throm Circulation, Vol.	malignar 914. ncrease \ culation, (i bin Recel 98, 175 A	-2,-3 and gy, 162(3 and phy ascular F2001), Voptor on the Abstract #	ysiologic Procoagol. 104, e Platel 2382, (*	ontrol i), pp. cal ulant et 1998)

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

40681

Sheet 2 of 2

	AS	Meli, Rosaria et al., Thrombin and PAR-1 activating peptide increase iNOS expression in cytokine-stimulated C6 glioma cells, <i>Journal of Neurochemistry</i> , 79(3), (2001) pp. 556-563.					
	AT	Nguyen, Quang-De et al., RhoA- and RhoD-dependent regulatory switch of Gα subunit signaling by PAR-1 receptors in cellular invasion, <i>FASEB Journal</i> , 16(6), (2002) pp. 565-576					
	AU	Remenar, Julius F., et al. Crystal Engineering of Novel Cocrystals of a Triazole Drug with 1,4-Dicarboxylic Acids, J.A. Chem Soc., Vol. 125 No. 28, (2003), pp.8456-8457.					
	AV	Roche, Nicolas et al., Effect of acute and chronic inflammatory stimuli on expression of protease activated receptors 1 and 2 alveolar macrophages, <i>Journal of Allergy and Clinical Immunology</i> , 111 (2), (2003), pp. 367-373.					
	AW	Schiller, H. et al., Thrombin as a survival factor for cancer cells: thrombin activation in malignant effusions in vivo and inhibition of idarubicin-induced cell death in vitro, <i>Int'l. J. of Clinical Pharmacology and Therapeutics</i> , 40 (8), (2002), pp. 329 – 335.					
	AX						
	AY						
	AZ	Tellez, Carmen et al., Role and regulation of the thrombin receptor (PAR-1) in human melanoma Oncogene 22, (2003), pp. 3130-3137.					
	ВА						
	ВВ	Vogel, S.M. et al, Abrogation of thrombin-induced increase in pulmonary microvascular permeability in PAR-1 knockout mice, <i>Physiol Genomics</i> , 4(2), (2000), pp. 137-145.					
	ВС						
EXAMINER	₹	DATE CONSIDERED					
*EXAMINE	R· In	nitial if reference considered, whether or not citation is in conformance with MPEP 609: Draw line					

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 40681_1